Epidemiology and cost of treatment of genital warts in Spain

Xavier Castellsagué¹, Catherine Cohet², Luis M Puig-Tintore³, Luis Olmos Acebes⁴, Jesus Salinas⁵, Maria San Martin⁶, Lusine Breitscheidel⁷, Vanessa Rémy⁸

Background: Genital warts (GW) are common and increasing in young people. Ninety percent of GW are due to Human Papillomavirus (HPV) types 6 and 11. The objective of this study was to assess the epidemiology and management costs associated with GW in Spain.

Methods: A 1-year (2005) retrospective observational study was performed among a sample of gynaecologists, dermatologists and urologists in six autonomous regions in Spain. Men and women with newly diagnosed, recurrent or resistant GW were included. We estimated the incidence (new and recurrent cases) and prevalence (also including resistant cases) of GW. Healthcare resource use were collected and combined with unit costs to assess the mean cost of GW management per patient. These figures were extrapolated to the 14- to 64-year-old Spanish population to estimate the total cost of GW management from the Third Party Payer (TPP) and societal perspectives.

Results: The overall annual incidence of GW was estimated at 160.4 cases per 100,000. Overall prevalence was calculated as 182.1 cases per 100,000, corresponding to 56,446 GW cases annually (14- to 64-year-old population). The mean management cost was €833 and €1056 per patient from the TPP and societal perspective, respectively. The overall annual cost was estimated at €47 million and €59.6 million, from the TPP and societal perspective, respectively.

Conclusion: This study provides a first overview of the burden of GW in Spain. A quadrivalent HPV vaccine that prevents HPV 6, 11, 16, 18 related diseases will have the potential to significantly decrease the socio-economic burden associated with GW in Spain.

Keywords: genital warts, epidemiology, costs, human papillomavirus, Spain

Introduction

Genital warts (condylomata acuminata) (GWs) are benign epithelial mucosal tumours caused by human papillomavirus (HPV), most commonly types 6 and 11; they are highly infectious and extremely prevalent. Annual prevalence is estimated at 1% of the sexually active population in the USA, and surveys indicate that it is increasing throughout Europe. HPV cannot be eradicated therapeutically, so the primary treatment aim is removal of symptomatic warts. However, such treatment is often long and painful, with a high number of recurrent and resistant cases. Retrospective studies have shown that the costs of treatment are considerable.

Vaccination is currently regarded as one of the most effective means of controlling HPV-related diseases. A prophylactic quadrivalent HPV vaccine (against types 6, 11, 16 and 18) was licensed in Europe in 2006; it has been shown to be up to 100% effective in preventing cervical cancer, precancerous cervical lesions and external genital lesions, including GWs.

To evaluate the benefits and public health impact of HPV vaccination, country-specific epidemiological and cost-of-illness data are needed. The epidemiology and treatment costs have been studied in a few European countries, but there are no published data for Spain. The objectives of this study were therefore to assess the incidence and prevalence of GWs in Spain, evaluate resource use, and estimate the direct and indirect costs of treatment from both the national health system (NHS) and societal perspectives.

Methods

Study design

This multicentre, retrospective, observational study was conducted in public settings in six autonomous regions of Spain (Andalucia, Cataluña, Valencia, Galicia, Madrid, País Vasco), accounting for 68% of the total population. The sample of clinicians and patients was assumed to be representative of Spanish clinical practice and population distribution. The study was conducted according to good pharmacoepidemiology practice, and the protocol was approved by an independent ethics committee at the Hospital Clinic of Barcelona.

Clinicians known to diagnose and treat GWs were invited to participate in the study. Data were obtained from gynaecologists and dermatologists for females, and from dermatologists and urologists for males. The study was divided into an epidemiological part and a resource utilization/cost part.

For the epidemiological study, investigators reviewed their medical records and reported aggregated data on the total number of patients seen in 2005, and the total number with GWs including newly diagnosed, recurrent and resistant warts. ‘Newly diagnosed’ in this instance means never having been diagnosed before with GWs. Patients with recurrent GWs had suffered a previous episode, whereas patients with resistant
GWs had lesions that remained despite treatment, resulting in chronic disease.

The resource utilization/cost study included patients aged 14–64 years (regarded as sexually active and therefore at risk) and excluded those who had participated in an interventional clinical trial during 2005, had only vestibular micropapillomatosis (women) or papillomatosis perlada (men), or had other non-HPV-related warts. Resource-use data for the treatment of GWs or associated medical complications were collected retrospectively from medical records. For patients with recurrent and resistant warts, the documentation period was 1 year (January–December 2005). For patients with newly diagnosed GWs, the documentation period was 6 months from the date of diagnosis (no later than 31 June 2005). Resource-use data were collected for investigator visits, visits to other physicians, procedures and examinations at physician visits, prescribed self-medication, hospitalizations and sick days.

**Sample size calculation**

Sample size was determined using a stratified sampling approach to ensure that a representative sample was analysed with regard to regional population size and the distribution of investigators according to medical specialty. Based on the assumption that the prevalence of GWs is low in Spain [0.5%, with an SD of 1% and a half-width confidence interval (CI) of 0.2% around the expected estimate], 200 investigators were required for the epidemiological study, of whom 50 were to be randomly selected to collect resource-use data for a total of 300 patients with GWs (100 newly diagnosed, 100 recurrent and 100 resistant). The sample size for the cost analysis was based on practical considerations to allow for valid statistical analyses with a sample size of 50 patients in each of the six analysis subgroups (i.e. two genders, three types of GW). It was therefore planned to randomly select 50 investigators who were asked to document retrospectively the resource use of six patients: two with newly diagnosed GW, two with recurrent GW and two with resistant GW.

On the basis of information from an expert advisory board about patients presenting with GWs, 80 gynaecologists, 85 dermatologists and 35 urologists were required for the epidemiological study. Of the 50 investigators in the cost study, 20 gynaecologists, 25 dermatologists and 5 urologists were required.

**Data analyses**

Observed incidence/prevalence in our investigator sample (percentage of patients per gender and per investigator specialty) were weighted by the proportion of patients treated per investigator type: basic assumptions were that 65% of males were diagnosed and treated by dermatologists and 35% by urologists, while 20% of females were diagnosed and treated by dermatologists and 80% by gynaecologists. Incidence relates to newly diagnosed and recurrent cases, while prevalence refers to resistant cases and all cases overall. Incidence and prevalence were retrieved from three Spanish databases: the Spanish Centre for Health Economics and Social Policy Studies (SOIKOS), a private database of costs for main medical procedures, hospital stays, diagnostic procedures and cost of health staff; the Official College of Physicians in Barcelona (Nomenclator), a public database with information on tariffs invoiced by physicians to private insurance companies; and the Official Pharmacists Colleges General Council (Base de Datos del Medicamento, BOT), a private database containing drug costs for a large collection of drugs in Spain. Costs are presented in 2005 Euros (€). The cost analysis involved calculating an adjusted mean total cost per patient based on the estimated distribution of gender and prevalence of GW types within the Spanish population. The weighting factors were based on results of the epidemiological study, and bootstrapping was performed.

The cost-of-illness analysis combined mean cost estimates for each of the six subgroups (males and females with new, recurrent or resistant GWs) with the annual number of cases estimated from the epidemiological study, to calculate the annual total costs of management. The analysis included sensitivity analysis, in which the costs of hospitalizations for all types of GWs were varied by 10% in both directions, and the incidence/prevalence used in the extrapolations were varied to their 95% CIs.

**Results**

**Epidemiology**

Due to an anticipated low response rate, 899 physicians were contacted. Of these, 137 completed data collection forms and 133 (66.5% of the required sample size) provided valid data for the epidemiological survey. Data for 7400 patients were collected, including 4795 new patients (incident) and 2605 with existing GWs (1733 recurrent, 872 resistant).

Overall estimated prevalence of all three types of GWs was 182/100 000 population (203/100 000 in males and 162/100 000 in females) (table 1). The estimated incidence of newly diagnosed GWs was 118/100 000 population (100/100 000 for females). Extrapolation to the total Spanish population, aged 14–64 years, estimated that 31 833 males and 24 613 females received treatment for GWs in Spain during 2005 (table 1).

**Resource utilization and cost assessment**

Forty-four investigators participated in the resource utilization/cost study, and data from 281 patients (99 newly diagnosed, 90 recurrent, 92 resistant; 128 males, 153 females) were included in the analysis. The mean age of patients was 31 ± 9 years (patients’ age distribution shown in figure 1 in Supplemental material). The majority of patients had

| Table 1 Estimated incidence and prevalence of GWS in Spain for the population aged 14–64 years in 2005a |
|---------------------------------|------------|----------|----------|----------|
|                                | New cases  | Recurrent cases | Resistant cases | Overall prevalence |
| Males                          |            |            |            |                      |
| Annual no. of cases            | 21 397     | 7 313      | 3 123     | 31 833              |
| Rate per 100 000               | 136.58     | 46.68      | 19.93     | 203.19              |
| Females                        |            |            |            |                      |
| Annual no. of cases            | 15 168     | 5 872      | 3 573     | 24 613              |
| Rate per 100 000               | 99.59      | 38.55      | 23.46     | 161.60              |
| Total                          |            |            |            |                      |
| Annual no. of cases            | 36 565     | 13 185     | 6 696     | 56 446              |
| Rate per 100 000               | 117.86     | 42.57      | 21.72     | 182.14              |

a: Estimates obtained by extrapolation (see Methods section).
acuminate warts (92.2%) or a combination of acuminate and papular warts (3.2%). Most patients had external warts (78.3%), with 19.6% reporting internal and external warts. One patient had internal warts only. Almost 15% of patients were immunocompromized (14.6%), and eight out of 153 females (5.2%) were pregnant.

Overall, the mean number of investigator visits per patient was 3.8 ± 1.5. Newly diagnosed patients made fewer visits than patients with recurrent warts who, in turn, made fewer visits than patients with resistant warts. Most patients reported physician visits with at least one procedure or examination (table 2). The most common procedure was application of imiquimod (Aldara®; 47.7%), followed by cryotherapy (44.1%). Almost all patients (95.7%) had a visual examination at least once. Frequent examinations applied only to females were Pap smears (80.4%) and colposcopy (69.3%). Approximately three-quarters of patients (74.4%) had medication prescribed at least once for the treatment of GWs. The majority were prescribed imiquimod or podophyllotoxin (Wartec®).

Overall, 49 patients (17.4%) were referred to another specialist, with the proportion in the newly diagnosed group (9.1%) being much lower than in the recurrent (22.2%) or resistant (21.7%) groups. Males were most frequently referred to a general practitioner, while females were most frequently referred to a gynecologist. Few patients underwent examinations (other than visual examinations) or procedures by other physicians. Other procedures included electrotherapy (10.2%), laser therapy (8.2%) and cryotherapy (6.1%).

In total, 45 patients (16.0%) were hospitalized. The median duration of hospitalization was 1 day (day clinic or one night in hospital), and the maximum duration was 30 days. More females than males were hospitalized at all disease stages (newly diagnosed, 17.7% vs. 4.2%; recurrent, 33.3% vs. 2.6%; resistant, 31.4% vs. 0%). Seven females required a second period of hospitalization for recurrent or resistant GWs.

Overall, sick leave was reported for 47 patients (16.7%), affecting 13 men (10.2%) and 34 women (22.2%), with a median duration of 7.5 days. In women, fewer newly diagnosed cases took sick leave (9.8%) than recurrent (23.5%) or resistant (33.3%) cases. No such pattern was observed for men: 8.3, 12.8 and 9.8%, respectively. In the newly diagnosed group, the median duration of sick leave was lower for women (1 day; range 1–4) than men (14 days; range 10–25), whereas the duration of sick leave was similar for men and women in the recurrent and resistant groups.

Of the 71 patients (25.3%) with related medical complications, 67 (94.4%) had an investigator visit documented. The most frequently reported complications were burning sensations (82.1%), erythema (73.1%) and oedema (37.3%). Five females (7.0%) had a single hospitalization, with a median duration of 10 days (range 1–35). Sick leave for complications was reported for 26 patients (36.6%), with a median duration of 25 days (range 2–70).

Overall, adjusted mean costs per patient were €1056 from the societal perspective and €833 from the NHS perspective (table 3). Maximum total costs per patient were €22 245 (societal) and €22 197 (NHS). Gender-adjusted mean costs per newly diagnosed patient were significantly lower than for those with recurrent or resistant GWs (figure 1). The higher costs for recurrent or resistant patients were mainly associated with hospitalization and sick leave. Adjusted mean costs for females (€1223 societal; €1040 NHS) were significantly higher than those for males (€927 societal; €673 NHS) (table 3), mainly due to higher hospitalization costs in females than in males. Medication and sick leave were the two largest cost factors from the societal perspective, accounting for 28% and 22% of costs, respectively. Physician visits, hospitalizations and medication were the major cost drivers from the NHS perspective, accounting for 23%, 22% and 22% of costs, respectively. Overall, sick leaves accounted for 15% of total cost from the payers’ perspective.

### Total burden of illness

In 2005, nearly 31 million people made up the 14- to 64-year-old Spanish population.17 Societal costs for the estimated 56 446 patients aged 14–64 years treated for GWs and medical complications during 2005 were estimated at €59.6 million (table 3). The cost estimate from the NHS perspective was €47.0 million. Sensitivity analysis showed that the base-case analysis was robust to relatively large variations in the costs of hospitalizations and incidence/prevalence disease estimates. Reducing and raising hospitalization costs by 10% gave NHS costs of €46.0 million and €48.0 million, respectively, and societal costs of €58.6 million and €60.6 million, respectively. Variation in the incidence/prevalence estimates to their 95% CIs gave NHS costs of €46.6 million and €47.4 million, respectively, and societal costs of €59.2 million and €60.1 million, respectively.

### Discussion

The burden of disease from GWs in Spain is substantial. During 2005, 31 833 males and 24 613 females aged 14–64 years were estimated to have been treated for GWs.

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**Table 2 Resource use for treatment of GWs or a medical complication in Spain**

<table>
<thead>
<tr>
<th>Resource use</th>
<th>Number of patients with GWs (%)</th>
<th>Number of patients with medical complications (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Investigator</td>
<td>281 (100)</td>
<td>67 (94)</td>
</tr>
<tr>
<td>Other physician</td>
<td>49 (17)</td>
<td>19 (27)</td>
</tr>
<tr>
<td>Procedure(s) during physician visits</td>
<td>257 (91)</td>
<td>29 (41)</td>
</tr>
<tr>
<td>Examination(s) during physician visits</td>
<td>278 (99)</td>
<td>38 (54)</td>
</tr>
<tr>
<td>Self-medication prescribed during physician visits</td>
<td>209 (74)</td>
<td>49 (69)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>45 (16)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Sick leave</td>
<td>47 (17)</td>
<td>26 (37)</td>
</tr>
</tbody>
</table>

**Table 3 Annual burden of GWs in the Spanish population, aged 14–64 years**

<table>
<thead>
<tr>
<th>Number of GWs cases</th>
<th>Adjusted mean cost per patient (€) (95% CI)a</th>
<th>Annual cost in Spain (million €)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NHS perspective</td>
<td>Societal perspective</td>
</tr>
<tr>
<td>Men</td>
<td>673.05 (666.23–688.24)</td>
<td>926.93 (917.30–941.14)</td>
</tr>
<tr>
<td>Women</td>
<td>1039.91 (993.89–1072.56)</td>
<td>1223.47 (1170.42–1264.71)</td>
</tr>
<tr>
<td>Total</td>
<td>832.50</td>
<td>1055.60</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NHS perspective</th>
<th>Societal perspective</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>21.42</td>
<td>29.51</td>
</tr>
<tr>
<td>Women</td>
<td>25.59</td>
<td>30.10</td>
</tr>
<tr>
<td>Total</td>
<td>47.01</td>
<td>59.61</td>
</tr>
</tbody>
</table>

a: 95% CI from bootstrapping with 1000 resamples.
Adjusted mean costs per patient of treatment and medical complications were €833 and €1056, with significantly higher costs for females (€1040 and €1223), from the NHS and societal perspectives, respectively. Estimated total costs were €47.0 million (NHS) and €59.6 million (societal).

This study is the most comprehensive evaluation of the burden of disease from GWs in Spain to date. In addition to evaluating the burden of disease from the perspectives of both the NHS and society as a whole, the study examined all disease states, gender differences, and wide-ranging resource use, including sick leave. Nevertheless, several limitations should be considered. Due to the convenient nature of our sample of investigators, there was a potential selection bias, as only investigators known to study advisors were recruited. Ideally, investigators would have been drawn randomly from a complete list of all eligible investigators in Spain, but no such list was available. Furthermore, there was some deviation from the stratified sampling approach, such that different regions had variable representation. It is notable that the regions included in the study are more industrialized, whereas some of the Spanish regions not included in the study are rural. The recent AFRODITA survey highlighted a marked difference in the sexual behaviour of populations in industrialized versus rural areas of Spain, which would explain regional differences in the prevalence of HPV infection and the incidence of HPV-related cervical cancer. The reported incidence of HPV-related cervical cancer is 9.03/100,000 in the general female population in Spain. More recent studies conducted in 2000 reported an annual incidence of external GWs of 107/100,000 population. More recent studies conducted in 2005 among gynaecologists reported an overall annual incidence of 114/100,000 in the general female population in France and an incidence of new and recurrent cases of 114 and 35/100,000, respectively, in Germany. In comparison, we have reported incidences of newly diagnosed GWs of 118/100,000 overall in Spain and of 100/100,000 in females. Besides methodological differences in study designs and healthcare systems, differences in the epidemiology of GW between countries might be explained by geographical and cultural variations in sexual behaviours.

The costs of treating GWs reported in this study are considerably higher than those reported in other studies based on reviews of patient records. In France, average treatment costs for women were recently reported as €342 (NHS) and €483 (societal). In the UK, average treatment costs from the payer’s perspective have been reported by Langley et al. as £222 for men and £211 for women (approximately €364 and €346 at 2000 exchange rates). Comparable costs for The Netherlands have been reported as €396 for men and €485 for women. In the USA, a database review among privately insured individuals reported average treatment costs per episode of $436. However, a modelling study in the USA has reported higher treatment costs of $1265–1304.

One explanation for the high costs in the present study might be the inclusion of medical complications, which incurred high hospitalization and sick-leave costs. Treatment costs for medical complications are not explicitly mentioned in any other published study, and few studies have considered sick leave. Caution is recommended, however, when attempting to compare data from different epidemiological and cost-of-illness studies because of differences in populations, study designs and methods, and public health settings, and the use of country-specific cost data.

In conclusion, this is the first epidemiological and cost-of-illness study of GWs conducted in Spain. The burden of GWs in Spain is substantial and the treatment of the disease results in considerable costs for the NHS, patients and employers, suggesting that an effective vaccination programme with the quadrivalent HPV vaccine would have substantial direct and indirect benefits for society. Although this study has estimated the economic burden of GWs on the Spanish NHS, the personal burden of the disease, in terms of physical, emotional and social health, remains to be further investigated. These study data should prove useful to healthcare decision-makers in evaluating the health and economic burden of GWs in Spain and the likely benefits of introducing a national HPV vaccination programme.
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Supplementary Data

Supplementary data are available at Eurpub online.

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Conflicts of interests

X. Castellsagué has received educational, research and travel grants and conference honorarium from Sanofi Pasteur MSD, Merck, Digene and GSK. L.M. Puig-Tintore is a consultant of the laboratories Sanofi Pasteur MSD and GSK. L. Olmos Acebes and J. Salinas received grants from Sanofi Pasteur MSD. C. Cohet, M. San Martin and V. Rémy are employees of Sanofi Pasteur MSD. L. Breitscheidel is an employee of Kendele.

Key points

- In the absence of previously published data, this study provides an estimate of the epidemiology of GWs and associated healthcare costs in Spain.
- This study shows that the high prevalence of GWs in Spain results in considerable costs to the Spanish healthcare system and Spanish society in general.
- Data from this study will be useful to healthcare decision-makers in determining the impact and benefits of introducing a national HPV vaccination programme.

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